UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA, Plaintiff, v. ELI LILLY AND COMPANY, IMCLONE LLC and BRISTOL MYERS SQUIBB COMPANY, Defendants.	)	Civil Action No. 2:15-cv-06133-PD

PLAINTIFF THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA'S
SUPPLEMENTAL CLAIM CONSTRUCTION BRIEF

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I. INTRODUCTION

The asserted '558 patent is technical and scientifically-dense. Yet, rather than provide clarity and explain the underlying scientific principles clearly, Defendants use this complexity to their advantage to confuse basic scientific premises. As they did in their briefs, Defendants continued to complicate the issues, misapply case law, and ignore highly relevant portions of the intrinsic evidence during their presentation at the *Markman* hearing.

First, with respect to the three "kinase activity" terms, Defendants' positions improperly import limitations from other claims and the specification into asserted claim 13. Claims must be given the full effect of their scope, and claim 13, which recites "kinase activity mediated by a p185 homodimer," should not be limited to "erbB kinase activity." Indeed the '558 specification refers to erbB kinase activities as well as intracellular kinase activities—both of which are mediated by p185. Additionally, for the "disrupts erbB kinase activity" and "erbB-mediated tumor" terms, Defendants conflate "disrupts tyrosine kinase activity" and "reduces the level of tyrosine phosphorylation," thereby twisting Dr. Craven's unrebutted expert testimony to create strawman indefiniteness arguments; as Dr. Craven explained, "disrupts kinase activity" does not necessarily translate to a reduction in the level of tyrosine phosphorylation, since other ongoing cellular processes affect the amount of phosphorylated proteins in a cell.

Second, Defendants attempt to limit claim 11 to only *in vitro* methods to manufacture a noninfringement argument, as Erbitux is of course administered to patients. But the language of claim 11 is not so limited, and both the patent specification and prosecution history make clear that claim 11 encompasses both *in vitro* and *in vivo* methods. Further, a proper application of claim differentiation and scientific principles, as explained by Dr. Craven and indicated by Defendants' own patents, supports this understanding.

Third, for "anti-cancer radiation," Defendants premise their argument on the incorporation of the entire Perez & Brady textbook. Defendants' fallacy in doing so is exposed by repeated disclosures in the '558 patent's specification limiting the invention to the use of conventional, standard radiation therapies, Defendants' own explanation of disavowal, Dr. Knox's unrebutted expert testimony, and Chapter 17 of Perez & Brady itself.

Defendants' attempts to narrow and broaden claim terms to manufacture invalidity and noninfringement positions ring hollow, for they belie basic claim construction canon and scientific realities. Accordingly, Penn requests that the Court reject Defendants' proposed constructions and adopt Penn's constructions.

II. LEGAL STANDARDS

"Claim construction requires a determination as to how a person of ordinary skill in the art would understand a claim term 'in the context of the entire patent, including the specification.'" *Trustees of Columbia Univ. in City of New York v. Symantec Corp.*, 811 F.3d 1359, 1362 (Fed. Cir. 2016) (citation omitted). Accordingly, "[i]n construing patent claims, the court must apply the same understanding as that of persons knowledgeable in the field of the invention." *Merck & Co. v. Teva Pharm. USA, Inc.*, 347 F.3d 1367, 1370 (Fed. Cir. 2003). This is because "[p]atents are written not for laymen, but for and by persons in the field of the invention." *Id.* (citation omitted).

While courts first look to the intrinsic record—including the claims themselves, the specification, and the prosecution history—"[e]xpert testimony can be useful 'for a variety of purposes, such as to provide background on the technology at issue, to explain how an invention works, [or] to ensure that the court's understanding of the technical aspects of the patent is consistent with that of a person of skill in the art." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042,

1052-53 (Fed. Cir. 2010) (finding no error in relying on uncontested testimony "to explain how the invention described in the intrinsic record functions" where the asserted patent related to the life sciences and drugs); *see also NeoMagic Corp. v. Trident Microsys., Inc.*, 287 F.3d 1062, 1074 (Fed. Cir. 2002) (ruling that the district court erred in claim construction and remanding for further evidentiary hearing, including expert testimony, on the meaning of a claim term "[g]iven the complex technology involved in this case"); *AFG Indus., Inc. v. Cardinal IG Co.*, 239 F.3d 1239, 1249 (Fed. Cir. 2001) ("we are reminded of the potential value of scientific testimony during claim construction hearings by the early statement of the Supreme Court that where the claims or specification 'contain technical terms or terms of art the court may hear the testimony of scientific witnesses to aid the court in coming to a correct conclusion'") (citation omitted).

Consequently, for patents involving complex science such as the '558 patent, it is routine for the parties to submit and the court to consider expert testimony. *See Eli Lilly and Co. v. Teva Parenteral Meds., Inc.*, No. 1:10-cv-1376, 2012 WL 2358102, at *9 (S.D. Ind. June 20, 2012) (relying on "Lilly's expert's opinion on the understanding of the term 'patient' by a person of ordinary skill in the art" and noting that "Defendants have not presented any other extrinsic evidence, in the form of expert reports, to support their proposed construction"); *Eli Lilly and Co. v. Teva Pharm. USA, Inc.*, No. 1:06-cv-1017, 2008 WL 2410420, at *6 (S.D. Ind. June 11, 2008) (evaluating expert testimony during claim construction including Lilly's citations to "the testimony of its expert, Dr. Ronald Thisted, in support of" its arguments).

III. DISPUTED CLAIM TERMS

a. "kinase activity," "kinase activity mediated by a p185 homodimer," and "disrupts kinase activity"

Claim Term	Penn's Construction	Defendants' Construction
"kinase activity"	the adding of a phosphate group by a protein to another protein	the adding of a phosphate group by an erbB receptor to a tyrosine residue of another protein
"kinase activity mediated by a p185 homodimer"	kinase activity mediated by p185 in its homodimeric form	the adding of a phosphate group by p185 to a tyrosine residue of another protein that occurs when p185 is in a homodimer
"disrupts erbB kinase activity"	disrupts the kinase activity of a member of the erbB protein family	reduces the level of tyrosine phosphorylation by erbB proteins

i. "Kinase activity" is not limited to erbB protein kinase activity

The parties have asked this Court to construe "kinase activity." Claim 13, the sole asserted claim, recites: "wherein the antibody inhibits **kinase activity mediated by a p185 homodimer**." ('558 patent, cl. 13 (emphasis added).) As Defendants have stressed, "any claim term that Your Honor's asked to interpret is to be given its ordinary and customary meaning, which is the meaning that the term would have to a person of skill in the art in question at the time of the invention." (Ex. 1, Markman Hearing Transcript ("Markman Tr.") at 107:8-13) (referencing *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005).) According to *Phillips*, "[i]t is a 'bedrock principle' of patent law that 'the claims of a patent define the invention to which the patentee is entitled the right to exclude.'" *Phillips*, 415 F.3d at 1312 (citation omitted). "Generally, claim terms are given the ordinary and customary meaning that would be ascribed to them by a person of ordinary skill in the field of the invention." *Takeda Pharm. Co. v. Sandoz, Inc.*, No. 12-00446, 2013 WL 2153673, at *4 (N.D. Cal. May 16, 2013) (citing *Phillips*, 415 F.3d at 1312-13).

Here, Defendants ignore the plain language of claim 13—"kinase activity"—and improperly attempt to read "erbB" into the "kinase activity" limitation of claim 13. Claim 11 recites "contacting the cell with an antibody that disrupts **erbB** kinase activity." ('558 patent, cl. 11 (emphasis added).) As Dr. Craven testified, "kinase activity" has a well-understood meaning to a person of ordinary skill in the art: it is the adding of a phosphate group by a protein to another protein. (*See* Markman Tr. at 10:2-12 ("[a] kinase is a protein that can attach a phosphate residue to another protein" and phosphorylation is "that process of adding a phosphate to a substrate"); D.I. 102-5 ("Craven Decl."), ¶ 27 ("[k]inase activity," therefore, "refers to the activity of such a protein.").) Indeed, both parties agree in their proposed constructions that "kinase activity" means "adding of a phosphate group" by a protein to "another protein."

Claim Term	Penn's Construction	Defendants' Construction
"kinase activity"	**the adding of a phosphate group** by a protein to **another protein**	**the adding of a phosphate group** by an erbB receptor to a tyrosine residue of **another protein**

The claimed "kinase activity" in claim 11 specifically references "**erbB** kinase activity," and thus claim 11 requires disruption of erbB proteins phosphorylating other proteins. This is not true for the broader term "kinase activity" as used in claim 13, other claims, and the patent specification.

Dependent claim 13 recites "[t]he method according to claim 11 wherein the antibody inhibits kinase activity **mediated by a p185 homodimer**." ('558 patent, cl. 13 (emphasis added).) Claim 13's reference to claim 11 requires infringement of claim 11 to infringe claim 13. In other words, for infringement of claim 13, there has to be **both** disruption of the "erbB kinase activity" recited in claim 11 **and** inhibition of "kinase activity" mediated by a p185 homodimer. Claim 13's dependence on claim 11, however, does not limit claim 13's "kinase activity" to only "erbB kinase activity."

If the inventors of the '558 patent had intended to limit claim 13 to "erbB kinase activity" as in claim 11, claim 13 would recite "wherein **said erbB kinase activity is that which is** mediated by a p185 homodimer" or "wherein **the erbB kinase activity is** mediated by a p185 homodimer." *Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1343 (Fed. Cir. 2008) ("In grammatical terms, the instances of 'said' [] in the claim are anaphoric phrases, referring to the initial antecedent phrase."). The inventors did so in several other claims. For example, claim 34 recites "[t]he method according to any one of claims 1 to 33, wherein **said** erbB protein mediated tumor is a p185 mediated tumor." ('558 patent, cl. 34 (emphasis added).) The use of a definite article ("said" or "the") in claim language is used to refer back to an initial antecedent basis in order to indicate that the term in a dependent claim has the same scope as in the independent claim. *See Takeda Pharm. Co.*, 2013 WL 2153673, at *6 ("where a claim term uses 'said' to refer back to an earlier phrase in the claim, the scope of the term will be the same as the scope of the earlier language."). The "said" or "the" language is missing from claim 13, and therefore the term "erbB kinase activity" in claim 11 does not provide antecedent basis for the "kinase activity" phrase in claim 13. Limiting "kinase activity mediated by a p185 homodimer" to erbB kinase activity would therefore be improper. *See Unwired Planet, LLC v. Apple Inc.*, 829 F.3d 1353, 1359 (Fed. Cir. 2016) ("We see no clear disavowal in the specification to justify importing a "voice channel" limitation into every claim given these differences between the claims.").

Defendants support their limitation of "kinase activity" to erbB kinase activity by pointing to disclosures in the '558 patent concerning erbB proteins. It is, however, improper to import limitations from the specification into the claims. *See Cont'l Circuits LLC v. Intel Corp.*, 915 F.3d 788, 797 (Fed. Cir. 2019), *cert. denied*, 140 S. Ct. 648 (2019) (explaining that courts must "avoid improperly importing limitations" from the specification into the claims and declining to read the

specification as imposing limitations); *Retractable Techs., Inc. v. Becton, Dickinson & Co.*, 653 F.3d 1296, 1305 (Fed. Cir. 2011) (noting that courts "strive to capture the scope of the actual invention, rather than strictly limit the scope of claims to disclosed embodiments"); *Phillips*, 415 F.3d at 1323 (noting courts should try to "avoid the danger of reading limitations from the specification into the claim" by focusing on "understanding how a person of ordinary skill in the art would understand the claim terms").

Moreover, Defendants do not dispute that the '558 patent discloses "kinase activity" of several different proteins, in addition to erbB proteins. These disclosures further undermine Defendants' narrowing constructions of "kinase activity" and "kinase activity mediated by a p185 homodimer". As admitted by Defendants, "there are lots of different types of kinases in the cell," such as "MAP kinase, the MEK kinase, the ERK kinase, the PI3 kinase." (Markman Tr. at 58:4-8, 62:1-6.) Additionally, after pointing out the '558 patent's specific disclosure regarding MAP kinases, Dr. Craven testified that activation of MAP kinases is mediated by p185 homodimers. (*Id.* at 21:13-22:21 (also testifying that "the inventors were keenly aware that there were protein kinases that were mediated by p185 that included MAP kinases and other kinases").) Tellingly, Defendants never challenged this testimony during the *Markman* hearing. Thus, it is undisputed that the '558 patent discloses that there are other non-erbB proteins with kinase activity within the cell, including MAP kinases, and that persons of ordinary skill in the art at the time of the Penn invention knew that p185 homodimers mediate the kinase activity of these intracellular proteins. (*Id.* at 58:4-8; 62:1-6; 22:3-23.) These undisputed facts are fatal to Defendants' attempt to limit "kinase activity" in claim 13 to erbB kinase activity.

Additional intrinsic and extrinsic evidence dooms Defendants' proposed construction for "kinase activity mediated by a p185 homodimer." Specifically, Defendants' construction requires

that the phosphorylation occur directly "by p185 . . . when p185 is in a homodimer." But Defendants ignore the disclosures in the patent specification regarding the kinase activity by other kinases as well as the understanding of a person of ordinary skill in the art of "kinase activity mediated by a p185 homodimer." As Dr. Craven testified, the inventors of the '558 patent knew about additional kinases and were "focused not only on manipulating kinase activity at the level of the erbB receptor, but also the entire signal transduction pathway that follows." (Craven Decl., ¶ 55.) Part of this entire signal transduction pathway includes kinase activity within heterodimeric or oligomeric complexes at the cell surface. As Dr. Craven testified, "[o]ligomeric complexes . . . would include multiple units of the erbB receptors in a larger complex." (Markman Tr. at 23:24-24:2.) p185 homodimers act as signaling partners and together with other members of the erbB family form these large oligomeric complexes to increase signaling activity. (*Id.* at 24:15-20.) The '558 patent clearly discloses formation of these complexes, indicating that the inventors were interested in active signaling to downstream (intracellular) components (such as MAPK) in addition to phosphorylation within oligomeric complexes at the cell surface—both of which can be mediated by p185 homodimers. (*Id.* at 24:21-25:3; '558 patent, 41:53-57, 43:34-39.) There is nothing in claim 13 or the rest of the '558 patent specification that requires kinase activity to be limited to phosphorylation performed directly by p185 homodimers. The proper construction of "kinase activity mediated by a p185 homodimer" therefore includes kinase activity within oligomeric complexes, *i.e.* kinase activities of other erbB dimers that were predicted in the '558 patent to associate with p185 homodimers to enhance signaling. (Craven Decl., ¶¶ 56-58.) As such, Defendants' construction is improperly restrictive by requiring "tyrosine phosphorylation by p185" that occurs when p185 is in a p185 homodimer.

At the time of the invention, a number of proteins and other tyrosine kinases involved in signal transduction mediated by p185 had already been identified. (*Id*., ¶¶ 55-58; '558 patent, 48:42-55.) Each one of these kinases was postulated to play a role in the signaling pathway leading from p185 on the cell surface to the nucleus, and a person of ordinary skill reading the '558 patent would have considered each of these "kinase activities" as mediated by activated p185. (Markman Tr. at 22:3-23; Craven Decl., ¶ 55.) These additional kinases, such as MAPK, that are undisputedly disclosed in the '558 patent, are encompassed by the term "kinase activity mediated by a p185 homodimer" in claim 13. (Markman Tr. at 35:20-36:13.) *See Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1062-63 (Fed. Cir. 2016) (*en banc*) (affirming that the term "keyboard" in claim did not exclude virtual keyboards because the specification disclosed physical and virtual keyboards); *Kaneka Corp. v. Xiamen Kingdomway Grp., Co.*, 790 F.3d 1298, 1303-05 (Fed. Cir. 2015) (finding district court's construction excluded embodiments in the specification and thus was improper); *MobileMedia Ideas LLC v. Apple Inc.*, 780 F.3d 1159, 1179-81 (Fed. Cir. 2015) (holding that district court erred in construing term from independent claim where the specification showed embodiments claimed by dependent claims that would be read out by court's construction). There is no requirement that the inventors explicitly name these additional kinases in claim 13 nor cite to specific passages within the specification in the claim. Rather, the claim must be interpreted in light of the specification and from the perspective of a person of ordinary skill in the art. Here, the specification and unrebutted expert testimony of Dr. Craven establish that Defendants' narrowing constructions of "kinase activity" and "kinase activity mediated by a p185 homodimer" are improper and Penn's proposed constructions are correct.

ii. Defendants' construction for "disrupts kinase activity" is wrong as a matter of science

In arguing for their construction of "disrupts kinase activity," Defendants muddy the waters by conflating the terms "tyrosine **kinase activity**" and "tyrosine **phosphorylation**" and erroneously fixating on "disrupts" versus "reduces the level of." The issue here is not the difference between "disrupts" and "reduces the level of," but instead, the difference between "disrupts kinase activity" and "reduces the level of tyrosine phosphorylation."

"Disrupts" is a plain English word that need not be construed. "In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words." *Phillips*, 415 F.3d at 1314; *see also Kenexa BrassRing, Inc. v. HireAbility.com, LLC*, 59 F. Supp. 3d 206, 221–22 (D. Mass. 2014) ("[I]f the ordinary meaning of a term can be readily understood by a layperson and adopting it would resolve the parties' dispute concerning interpretation, there is no requirement that a court provide additional language construing a claim."). "Disrupts" should be given its plain and ordinary meaning, and there is no evidence in the intrinsic record that the term "disrupts" should mean anything else.

The definition of "disrupts" according to Merriam-Webster is "to **interrupt** the normal course or unity of."[1] Dr. Craven's testimony has remained consistent with that meaning. (Markman Tr. at 16:2-6 ("Another way of saying disrupting kinase activity might be to **interfere with** the activity or **block** the activity of the kinase.") (emphasis added).)[2] Though "disrupts" is a

[1] *See* https://www.merriam-webster.com/dictionary/disrupts (emphasis added).

[2] While Penn maintains that "disrupts" does not need to be construed, if the Court decides otherwise, "interferes with" or "blocks" are acceptable alternatives consistent with the intrinsic and extrinsic evidence.

well-understood, commonplace word, Defendants attempt to manufacture an indefiniteness argument by twisting Dr. Craven's words. (*Id.* at 67:14-19 ("They can't tell you what the difference is between disrupting and reducing… Your Honor is aware of the law about indefiniteness. The patent has to provide reasonable certainty regarding the scope of the asserted claims, and their construction simply doesn't do that.").) This argument has no merit.

A patent is invalid for indefiniteness only if "its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 897-99 (2014). Moreover, any fact critical to a holding on indefiniteness must be proven by the challenger by clear and convincing evidence. *Intel Corp. v. VIA Techs., Inc.* 319 F.3d 1357, 1366 (Fed. Cir. 2003). In this case, Defendants would need to prove, by clear and convincing evidence, that a person of ordinary skill in the art would not understand the meaning of "disrupts erbB kinase activity" in the context of the '558 patent. *Id.* They have utterly failed to meet this burden.

First, Dr. Craven testified that one skilled in the art reading the '558 patent would understand what "disrupts" means and noted that "disrupts" and "reduces" are similar if one is talking about the same endpoint. (Markman Tr. at 32:4-15.) Contrary to Defendants' representations, Dr. Craven and Penn agree with Defendants that disruption of erbB **kinase activity** would result in reduction of erbB **kinase activity.** (*Id*. at 32:6-10, 77:8-10.)

Second, Defendants' attorney indefiniteness arguments fail to cite to any requisite supporting expert testimony. *See Hand Held Prods., Inc. v. Amazon.com, Inc.*, No. 12-768, 2014 WL 2873902, at *16 (D. Del. June 24, 2014), *report and recommendation adopted*, 2014 WL 5779416 (D. Del. Nov. 5, 2014) (rejecting indefiniteness argument where infringing party

provided "no expert testimony in support of its indefiniteness argument" and "[relied] instead on attorney argument"); *Green Pet Shop Enters., LLC v. European Home Design, LLC*, No. 17-CV-6238, 2019 WL 1172069, at *3 (S.D.N.Y. Mar. 13, 2019) (rejecting infringer's indefiniteness argument because of, among other things, "the absence of competing expert evidence"). As is the case with every term in dispute in this case, Defendants have failed to provide any expert testimony to rebut Dr. Craven, support their claim constructions, or support this last-ditch indefiniteness argument.

In essence, Defendants attempt to confuse the Court by focusing on the terms "disrupts" and "reduces" and creating indefiniteness arguments around those well-understood terms to divert from the inexplicable fact that Defendants are using the terms "disrupts kinase activity" and "reduces the level tyrosine phosphorylation" interchangeably. As explained by Dr. Craven, "disrupting kinase activity" and "reducing the level of tyrosine phosphorylation" cannot be equated, because there are ways to reduce levels of tyrosine phosphorylation other than by disrupting tyrosine kinase activity. (Markman Tr. at 32:4-14, 39:23-40:4.) As Dr. Craven testified, levels of tyrosine phosphorylation are impacted by other processes in cells in addition to tyrosine kinase activity. (*Id.*) Defendants have never disputed this scientific truth, nor can they.

Nor have Defendants pointed to any intrinsic evidence supporting their use of "tyrosine phosphorylation." During the *Markman* hearing, Defendants purported to cite to the specification of the '558 patent to support their construction of "reduces the level of **tyrosine phosphorylation**." (*Id.* at 64:24-66:15.) The passages Defendants point to, however, only refer to "elevated tyrosine **kinase activity**." (*Id.*) Not one of these passages mentions "tyrosine phosphorylation."

> - "Such dimerization of overexpressed p185 leads to elevated tyrosine **kinase activities** which is associated with the transformed phenotype. **Disruption of tyrosine kinase activity,** such as by inhibiting dimer formation between monomeric components, results

in a cytostatic effect on the tumor cells." ('558 patent, 23:57-67; Markman Tr. at 65:8-11 (discussing this passage from the patent) (emphasis added).)

- "Such dimerization of ΔEGFR leads to elevated tyrosine **kinase activities** which is associated with the transformed phenotype. **Disruption of tyrosine kinase activity,** such as by inhibiting dimer formation between monomeric components, results in a cytostatic effect on the tumor cells." ('558 patent, 24:1-12; Markman Tr. at 66:13-15 (citing this passage) (emphasis added).)

Defendants have not pointed to a single citation in the intrinsic record that refers to "elevated tyrosine phosphorylation", let alone "elevated levels of tyrosine phosphorylation." Additionally, these passages further support Penn's proposed construction of "disrupts kinase activity," as they provide explanations of the claimed disruption to a person of ordinary skill in the art.

b. "erbB mediated tumor"

Penn's Construction	Defendants' Construction
tumor whose transformed phenotype is associated with tyrosine kinase activity by one or more members of the erbB family of receptors	tumor whose transformed phenotype requires an elevated level of tyrosine phosphorylation by erbB proteins in tumor cells

Defendants' proposed construction and supporting arguments fail due to the same fallacy identified above—"tyrosine kinase activity" does not necessarily result in an "elevated level of tyrosine phosphorylation." As explained above, Defendants' citations to the intrinsic record refer only to "tyrosine kinase activity," and Defendants fail to provide any citation to the '558 patent discussing elevated levels of tyrosine phosphorylation. This is because, as explained by Dr. Craven, levels of tyrosine phosphorylation are impacted by other processes in cells, in addition to tyrosine kinase activity, and thus elevated tyrosine kinase activity does not necessarily result in an elevated level of tyrosine phosphorylation. (Markman Tr. at 39:4-9, 39:23-40:17; Craven Decl., ¶ 52.) It is therefore improper to hinge the construction of "erbB mediated tumor" on levels of

"tyrosine phosphorylation." Such a construction contravenes the intrinsic evidence and scientific reality.

On the other hand, Penn's proposed construction is supported by the intrinsic and extrinsic record. The '558 patent discloses that an "erbB-mediated transformation," by which a cell becomes cancerous, (1) "is mediated by tyrosine kinase activity" related to a member of the erbB gene family, such as EGFR, and (2) results from the "express[ion of] a member of the erbB gene family." ('558 patent, 11:21-38.) Penn's proposed construction consequently draws directly from this disclosure, as a person of ordinary skill in the art would understand that an "erbB mediated tumor" is "a tumor whose transformed phenotype is associated with tyrosine kinase activity by one or more members of the erbB family of receptors." (Craven Decl., ¶ 32.) Thus, while Defendants' construction is contrary to the '558 patent, Penn's comports with the disclosures within it.

c. "contacting the cell with an antibody" and "said tumor cell being from an erbB mediated tumor"

Claim Term	Penn's Construction	Defendants' Construction
"contacting the cell with an antibody"	administering an antibody that interacts with the cell	placing the antibody into direct physical contact with the cell rather than administering the antibody intravenously
"said tumor cell being from an erbB-mediated tumor"	the tumor cell is from a tumor whose transformed phenotype is associated with tyrosine kinase activity by one or more members of the erbB family of receptors	a transformed tumor cell removed or derived from an erbB mediated tumor

The parties' dispute boils down to the question of whether claim 11 covers both *in vitro* (in the laboratory) and *in vivo* (in a patient) methods. Defendants agree with Penn and Dr. Craven that claim 11 covers *in vitro* methods, but rely on obfuscation to narrow claim 11 to only those methods. (Markman Tr. at 85:10-12.) Nothing in the claim language supports such a narrow

interpretation, and Defendants' leaps of logic contradict intrinsic and extrinsic evidence as well as general practice pertaining to life sciences patents.

Defendants' cross examination of Dr. Craven focused on comparing the language of claim 11 with claim 1. Both claims are reproduced below:

11. A method for inhibiting proliferation of a tumor cell, said tumor cell being from an erbB mediated tumor, which method comprises steps of: (a) contacting the cell with an antibody that disrupts erbB kinase activity said disruption having a cytostatic effect on the tumor cell; and (b) thereafter exposing the tumor cell to an effective amount of anti-cancer radiation.	**1.** A method of treating an individual who has an erbB protein mediated tumor which method comprises steps of: (a) administering to said individual an antibody which inhibits formation of erbB protein dimers that produce elevated tyrosine kinase activity in a tumor cell, said inhibition having a cytostatic effect on the tumor cell; and (b) thereafter exposing said individual to a therapeutically effective amount of anti-cancer radiation.

('558 patent, cls. 1 and 11.) Looking at the language of claim 11, nothing in the claim excludes the use of the claimed method on patients. Claim 11 is broader than independent claim 1; based on plain meaning of the claim language, claim 11 can apply to *in vitro* and *in vivo* methods. (Craven Decl., ¶¶ 35-41.) Defendants fail to cite to any portion of the specification or prosecution history that allegedly constitutes a disavowal of *in vivo* methods being encompassed by claim 11. Indeed, the specification directly refutes Defendants' argument that the term "effective amount" in claim 11 (as opposed to "therapeutically effective amount" in claim 1) excludes treatment of individuals from the scope of claim 11. (*See* '558 patent, 15:50-52 ("An **effective amount** of such combinations **are administered to an individual** who is identified as suffering from or being susceptible to erbB-associated tumors.") (emphasis added).) Thus, Defendants' cross examination highlighting the use of "therapeutically effective amount of anti-cancer radiation" in claim 1 and

"effective amount of anti-cancer radiation" in claim 11 is of no import. (Markman Tr. at 85:17-86:14.)

Defendants' argument is contrary not only to the specification's use of "effective amount" to refer to the treatment of patients, but also to logic, Federal Circuit precedent, and the use of "effective amount" in life sciences and pharmaceutical patents, including Defendants' patents.

An "effective amount" of anti-cancer radiation can be administered to a person, and the Federal Circuit has held that "'effective amount' is a common and generally acceptable term for pharmaceutical claims." *Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1383-84 (Fed. Cir. 2003). Moreover, the Federal Circuit and other district courts have construed "effective amount" in patents and claims directed to *in vivo* methods. For example, with respect to one of Defendant Lilly's own patents, the Southern District of Indiana construed "effective amount" in conjunction with the use of the claimed compound or drug on patients. *Eli Lilly & Co. v. Apotex, Inc.*, No. 1:17-cv-02865, 2019 WL 7049799, at *9-10 (S.D. Ind. Dec. 23, 2019). In its analysis, that court reasoned, "[i]mmediately following the specification's definitional language for 'effective amount,' the specification explains, '[f]or example, an effective amount of an antifolate drug that is administered in an effort to reduce tumor growth is that amount which is required to reduce tumor growth.'" *Id.* Despite using the term "effective amount," the purpose of the invention was "to provide a therapeutic benefit to a patient in need thereof." *Id.* Thus, Defendants' emphasis on the difference of "therapeutically effective amount" and "effective amount" is a red herring. Claim 11, while using "effective amount," covers *in vitro* and *in vivo* methods.

There is no other language in claim 11 that limits the claim to only *in vitro* methods. For example, "contacting the cell" has also been used within Defendants' own patents to pertain to *in*

vivo methods. In U.S. Patent No. 8,535,684, which is assigned to Defendant Lilly, claims 2 and 3 equate "administering" a protein to a mammal with "contacting cells of said mammal:"

> **1.** A method of inhibiting the infectivity of HIV in mammalian cells, comprising: selecting mammalian cells in need of inhibition of HIV infectivity and ***contacting said cells*** with an effective amount of an antibody that binds preferentially to Robo1 protein.
>
> **2.** The method of claim **1**, wherein said selecting is accomplished by selecting a mammal in need of reducing the infectivity of HIV and ***said contacting is achieved by administering said antibody to said mammal***.
>
> **3.** The method of claim **1**, wherein said method comprises ***administering to said mammal*** a Robo 1 protein which induces said mammal to produce antibodies which bind preferentially to Robo1 protein, ***thereby contacting cells*** of said mammal with said antibodies produced.

(Ex. 2 at 55:20-56:24 (emphasis added).) Defendant BMS's U.S. Patent No. 5,877,210 ("the '210 patent") uses "contacting" analogously to claim 11. Dependent claims 17 and 18 of the '210 patent, respectively, claim "A method for inhibiting proliferation of B cells comprising the step of contacting proliferating B cells with the conjugate of claim 1" and "A method for inhibiting proliferation of B cells comprising the step of contacting proliferating B cells with the conjugate of claim 3." (Ex. 3 at 67:50-55.) As the '210 specification explains, where the claimed methods "comprise[] the step of contacting the proliferating malignant cells" with a compound, that "compound is administered." (*Id.* at 24:48-61.) According to the '210 patent, "[t]he compositions can be administered using conventional modes of administration including, but not limited to, intravenous, intraperitoneal, oral, or intralymphatic" and other "routes of injection" can also be used. (*Id.* at 24:62-65.) The same is true of the '558 patent—here too, "contacting" means "administered." As explained in Penn's briefing, during prosecution, the examiner found all the claims, including claim 11, to be directed to methods of treating patients. Thus, "contacting" in claim 11 includes administering to a patient. Defendants' own use of "contacting" in their own

claims demonstrates that such language is common in life sciences and pharmaceutical patents. Again, their arguments evidence an improper effort to manufacture noninfringement arguments and inject confusion where none exists.

Additionally, claim differentiation does not apply to claim 1 and claim 11. As discussed in Penn's briefs, Defendants incorrectly applied claim differentiation to argue based on claim 1 that claim 11 applies only to *in vitro* methods. Claim differentiation, however, requires that courts do not improperly narrow independent claims by reading in limitations present in dependent claims. *See Phillips*, 415 F.3d at 1314-15. Claim 1 and claim 11 are both independent claims, and thus the doctrine of claim differentiation does not apply. Moreover, it is readily apparent that they are different in scope: claim 1 is directed to "an antibody which inhibits formation of erbB protein dimers," while claim 11 is directed to "an antibody that disrupts erbB kinase activity." (*Compare* '558 patent, cl. 1 *with id.*, cl. 11; *see also* Craven Decl., ¶¶ 35-40.) Accordingly, Defendants' claim differentiation argument fails. It is additionally telling that Defendants provided *no* rebuttal to these arguments presented in Penn's responsive brief.

Finally, Defendants did not touch any of Dr. Craven's testimony on direct examination. As Dr. Craven explained, the "purpose of the '558 patent is to treat individuals with cancer" and not "to come up with an *in vitro* technique on cells that are isolated in culture." (Markman Tr. at 82:15-25.) Additionally, Dr. Craven's unrebutted expert testimony explains how Defendants' proposed constructions contravene what scientists would do in practice. Defendants' proposed construction of "contacting the cell with an antibody" as "placing the antibody into direct physical contact with the cell" ignores the reality that "[t]here would be many, many molecules of antibody in the solution, and you would add them to many, many cells," such that one "would not," and could not "take one antibody and try to somehow attach it to a cell." (*Id.* at 82:2-14.) Similarly,

for "said tumor cell being from an erbB-mediated tumor," Defendants' proposed construction injects the requirement "to remove a cell from a tumor and do something to it to affect its growth or its survival." (*Id.* at 83:5-15.) This, however, "isn't something people typically do" as they would not "remove a single tumor cell from an individual and try to treat it." (*Id.*)

Defendants' manipulation of claim 11 into one that solely covers *in vitro* methods is refuted by the intrinsic evidence, Federal Circuit precedent, Defendants' own patents, and scientific reality. Accordingly, Penn respectfully requests that the Court reject Defendants' proposed constructions for these terms and instead adopt Penn's.

d. "cytostatic effect"

Penn's Construction	**Defendants' Construction**
inhibition or suppression of cell growth and multiplication	plain and ordinary meaning

Both parties agree that the term offered for construction is "cytostatic effect," not "having a cytostatic effect" or "effect." And, after questioning from the Court during the *Markman* hearing, Defendants' counsel *thrice* agreed that a "cytostatic effect" has the plain and ordinary meaning of "inhibition or suppression of cell growth and multiplication" and ultimately agreed to Penn's proposed construction. (Markman Tr. at 98:4-13, 99:3-5, 100:3-5, 102:21-25.) Defendants' belated concession is consistent with their proffered construction of "cytostatic effect" before the stay of this case, which used the same language as Penn's presently proposed construction and distinguished inhibition or suppression of cell growth from killing cells. (*Id.* at 101:1-11.)

Defendants, during the hearing, ultimately also distinguished a "cytostatic effect" from a "cytotoxic effect." (*Id.* at 103:2-7.) Nonetheless, during their arguments, Defendants confusingly focused on whether an antibody can have both a "cytostatic effect" and a "cytotoxic effect" and still fall within the scope of the asserted claim. This categorization is immaterial as to the asserted

claim, however, because while Defendants' arguments focused on effects on a population of tumor cells, (*see, e.g.*, *id.* at 97:5-9), the claim is focused on "**a** tumor cell." ('558 patent, cl. 11 (emphasis added).) As Penn and Dr. Craven explained, an antibody cannot both inhibit or suppress the growth of a cell and kill the cell. Instead, as to a single cell, the antibody does one or the other. Defendants' avoidance of the claim language and silence as to this argument is telling. Thus, as the parties have agreed, the Court should construe "cytostatic effect" as "inhibition or suppression of cell growth and multiplication."

e. "anti-cancer radiation"

Penn's Construction	**Defendants' Construction**
conventional, established radiation therapies used at the time of the filing to treat cancer patients	radiation that kills cancer cells, regardless of the type or source of the radiation

Defendants premise their critique of Penn's construction for "anti-cancer radiation" on the '558 patent's supposed incorporation of the entire Perez & Brady textbook. Defendants' arguments, however, belie Federal Circuit precedent and the intrinsic and extrinsic record before the Court.

Claims "must be read in view of the specification of which they are a part." *Phillips*, 415 F.3d at 1315. "When a patent . . . describes the features of the 'present invention' as a whole, this description limits the scope of the invention." *Verizon Servs. Corp. v. Vonage Holdings Corp.*, 503 F.3d 1295, 1308 (Fed. Cir. 2007). Accordingly, a claim's scope may be properly narrowed or disavowed based on the intrinsic record, including statements in the specification regarding what the invention relates to. *Techtronic Indus. Co. v. Int'l Trade Comm'n*, 944 F.3d 901, 907-08 (Fed. Cir. 2019) ("It is axiomatic that, where the specification 'describes the present invention as having [a] feature,' that representation may disavow contrary embodiments.") (citation omitted); *Forest Labs., LLC v. Sigmapharm Labs., LLC*, 918 F.3d 928, 932-33 (Fed. Cir. 2019) (limiting the scope

of a claimed composition based on the intrinsic record including statements such as "[t]he invention relates to. . . ."). Moreover, contrary to Defendants' statements at the Markman hearing, (Markman Tr. at 110:9-11, 111:25-112:3), "rigid formalism," such as "my invention does not include _____," "is not required" to indicate disavowal. *Astrazeneca AB v. Mutual Pharm. Co.*, 384 F.3d 1333, 1336-42 (Fed. Cir. 2004). Instead, "the patentee's choice of preferred embodiments can shed light on the intended scope of the claims." *Id.*

Turning to the facts here, the '558 patent mentions the Perez & Brady textbook once, in the context of developing known "appropriate radiotherapeutic regimens" and gamma radiation:

> In some preferred embodiments, treatment with pharmaceutical compositions according to the invention is preceded by surgical intervention. In preferred embodiments, the radiotherapy follows administration of pharmaceutical compositions according to the invention. In preferred embodiments, the radiation therapy using **gamma radiation** is provided following the administration of compositions which convert radiation resistant tumors, radiation sensitive. **Those skilled in the art can readily formulate an appropriate radiotherapeutic regimen**. Carlos A Perez & Luther W Brady: Principles and Practice of Radiation Oncology, 2nd Ed. JB Lippincott Co, Phila, 1992, which is incorporated herein by reference describes radiation therapy protocols and parameters which can be used in the present invention.

('558 patent, 18:6-19 (emphasis added).) Though the inventors incorporate Perez & Brady here, this sentence cannot be read in a vacuum, as Defendants suggest. Instead, the entire specification must be considered to determine whether experimental anti-cancer radiation therapies fall outside the scope of the '558 patent's invention.

As highlighted by Penn, the '558 patent clearly discloses that the invention pertains to conventional and established radiation therapies used to treat patients at the time of the filing of the patent. For example, the '558 patent states:

- "Inhibition mediated by the introduction of mutant p185neu receptors causes synergistic growth inhibition when combined with **conventional cytotoxic agents such as gamma-irradiation**. **The present invention provides methods of**

treating many epithelial solid tumors since the methods of the invention complement the use of already established treatment modalities." (*Id.* at 18:48-54.)

- "According to aspects of the present invention, after administering the composition that comprises an active agent which causes disruption of the kinase activity associated with the multimeric receptor ensemble; the individual is then exposed to a therapeutic amount of **gamma radiation**. . . . Thus, once the active agent inhibits the kinase activity, exposure to radiation may follow suit. **Gamma radiation is delivered according to standard radiotherapeutic protocols using standard dosages and regimens**." (*Id.* at 26:7-27.)

- "Inhibition of growth factor-mediated signaling has been correlated with increased sensitivity to **standard anti-cancer reagents** in a number of systems." (*Id.* at 19:38-40.)

- "In particular, inhibition of the EGFR in malignant human glioma cells can increase the degree of growth arrest and apoptosis observed after DNA damage caused by **X-rays**." (*Id.* at 54:18-21.)

(Emphasis added). Thus, the only anti-cancer radiation disclosed by the inventors of the '558 patent is an "already established treatment modality," such as, for example, gamma radiation and x-rays. Accordingly, as Dr. Knox's unrebutted testimony provides, a person of ordinary skill would understand that the '558 patent's claims do not cover experimental radiation therapies. (D.I. 102-1, Knox Decl., ¶¶ 29-34.) Hence, any disclosure of such a therapy, including RIT, in Perez & Brady falls outside the scope of the '558 patent.[3]

Indeed, a review of Chapter 17 of the Perez & Brady textbook supports this understanding. Chapter 17 contains no clinical protocols or parameters for RIT, such as dosing guidelines or treatment plans. (Appx. 64 at A1328-39.) Accordingly, "those skilled in the art" would not be

[3] During the hearing, Defendants cherry-picked excerpts of Dr. Knox's deposition testimony to support their argument that the inventors incorporated the entire Perez & Brady textbook with no carveouts. Read in its full context, Dr. Knox's testimony is unfavorable to Defendants' position. For example, Dr. Knox provided testimony consistent with her declaration that Perez & Brady's chapters regarding investigational therapies in various stages of development, such as RIT, would fall outside the scope of the '558 patent due to the patent's emphasis on already established and conventional treatments, according to a person of ordinary skill in the art. (Ex. 4, Knox Tr. at 62:23-65:6.)

able to "readily formulate an appropriate radiotherapeutic regimen" for RIT using Perez & Brady.

Importantly, when questioned by the Court during the *Markman* hearing about the passages in the '558 patent's specification that state, for example, "**The present invention provides** methods of treating many epithelial solid tumors since the methods of the invention complement **the use of already established treatment modalities,**" Defendants' counsel simply asserted, "That's not disavowal." (Markman Tr. at 117:22-119:16.) This, however, as explained above, contradicts Federal Circuit precedent and Defendants' own explanation regarding disavowal:

> "Now, let's talk about disavowal. . . . You have to make some statement in your specification that states "**the present invention requires**" or "**the present invention is**" or "all embodiments of the present invention are," and you disclaim certain territory."

(*Id.* at 111:15-24 (emphasis added).) As the above-quoted passages from the specification demonstrate, the inventors consistently characterized the invention as the use of conventional and established anti-cancer radiotherapeutic protocols after administration of an anti-erbB antibody, thereby disavowing the use of experimental radiation therapies.

In sum, Defendants fail to provide any contrary testimony to Dr. Knox's and to rebut Penn's arguments that experimental RIT falls outside the scope of the '558 patent's disclosures regarding "anti-cancer radiation." Instead, Defendants rely on unsupported attorney argument stating that "at the time of this patent, radioimmunotherapy, RIT, was well-known to a person of ordinary skill in the art." (*Id.* at 109:11-12.) This statement carries no weight, because, not only does it contradict Chapter 17 of Perez & Brady and the characterization of RIT therein, but also Defendants' counsel's say-so does not make RIT a conventional and established form of therapy at the time that was used to treat patients. Accordingly, Penn requests that the Court reject Defendants' overly-broad proposed construction.

IV. CONCLUSION

Based on the parties' claim construction briefing, arguments during the *Markman* hearing, and the foregoing, Penn respectfully requests that the Court adopt Penn's proposed constructions.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I, Jonathan G. Graves, hereby certify that on this date I caused a true and correct copy of the foregoing to be filed with the Clerk of the Court using the CM/ECF system, which in turn sent notifications of such filing to all counsel via electronic mail.

Dated: February 21, 2020

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